Defense Technical Information Center
Compilation Part Notice

ADP010455

TITLE: Non Benzodiazepines Hypnotics: Another Way
to Induce Sleep

DISTRIBUTION: Approved for public release, distribution unlimited

This paper is part of the following report:

TITLE: Individual Differences in the Adaptability
to Irregular Rest-Work Rhythms/Status of the Use
of Drugs in Sleep-Wakefulness Management [les
Differences entre individus concernant les
facultes d'adaptation aux rythmes irreguliers
activite-repos/Le point sur l'utilisation des
medicaments pour la gestion des periodes
veille-sommeil]

To order the complete compilation report, use: ADA388183

The component part is provided here to allow users access to individually authored sections
of proceedings, annals, symposia, ect. However, the component should be considered within
the context of the overall compilation report and not as a stand-alone technical report.

The following component part numbers comprise the compilation report:
ADP010453 thru ADP010473

Non Benzodiazepines Hypnotics: Another Way to Induce Sleep

Captain Antonios Kodounis
251 Air Forces Hospital
3, Kanellopoulou Ave.
Goudi, Athens
Greece

Summary :

The third generation hypnotics, zolpidem and zopiclone can be used to optimize rest periods during sustained operations and help the military personnel.
This is possible because these drugs provide a good quality of sleep, without residual effects in the morning after administration.
A literature review of the possible limitations of use of these drugs in pilots has been presented.

1. Introduction

Technological advances have improved the ability of military Air Force crews to withstand the operational demands of increased workload in a hostile environment (60). The 1986 air raids in Libya (59) and the Falklands war have shown, however, that physical and psychological fatigue of the pilots and ground support crews can reduce operational success. This is especially the case when operations take place from aircraft carriers in extreme conditions of frequent flights and little rest, including flights 24 hours a day, for long periods of time and lack of soundproof buildings.

Mc Couley (39) has claimed that crew tiredness is a common denominator of human errors responsible for accidents during the flight and that 60% of accidents happen during approach and landing procedures. One study (53) examined the relationship between alertness and successful landing. The results have showed that reduced alertness represents an important factor in several accidents during approach and landing. A number of studies (10) have shown that aircrews taking part in mid and long range flights have anomalies of the sleep-wakefulness cycle, which are caused by disruption of circadian rhythm. Another factor that disrupts circadian rhythms is the conduct of nocturnal operations, a current problem as the majority of NATO attacks on Yugoslavia take place in the night-time. Dealing with crew tiredness is therefore vital in accident prevention. To achieve this, it is necessary to overcome the sleep difficulties caused by operational stress, hostile environment and disruption of circadian rhythms.

Hypnotic drugs can help to deal with these difficult situations. The perfect hypnotic should act rapidly, have a short duration of action, not lead to dependence and have no residual effect so that any impairment is not carried into the next day.

It is also important to preserve the architectural structure of normal sleep. Drugs should not reduce sleep stages III and IV, which are essential for rest. They should also not interfere with R.E.M. sleep during which dreams occur, as dreams play an important role in psychological well being and are vital for effective rest.

The non-benzodiazepine 3rd generation hypnotics (zolpidem, zopiclone) are close to the above characteristics of the perfect hypnotics as existing studies prove that they preserve good sleep quality and no suppression of higher cognitive functions 6 hours after their administration.

Before reviewing the relevant literature in more detail, let us see first what exactly sleep and insomnia are. It should be noted that it is not uncommon for individuals to complain about lack of sleep and impaired daytime performance even though there is no objective evidence of insomnia from sleep recordings. This is known as pseudoinsomnia, or sleep state misperception (56).

2. Sleep and Insomnia

Even though we spend more time sleeping than in any other activity, it is difficult to define exactly what sleep is and what precise purpose it serves. We experience sleep as a loss of consciousness of our environment and we feel intuitively that it must fulfil some restorative function. Many circadian rhythms are linked tightly to our sleep/wake cycle. An adequate period of sleep at night is necessary in order to feel refreshed and effective the next day. It has been demonstrated that, while we sleep, bones grow (61), cells divide (12), wounds heal (51) and that hormones, such as growth hormones, are released (67). Sleep seems to facilitate the reinforcement of long-term memory traces (18), but is associated with a general slowing of brain activity and metabolism (38).

Arousal and wakefulness seem to be related to a high level of electrical activity within the cerebral cortex (27). When this electrical activity wanes, drowsiness and sleep set in. It seems that cortical activity is maintained by stimulatory input from a structure in the brainstem called the Reticular Activating System (RAS) (27, 63). Activation of the cortex by the RAS elicits awakening and vigilance. The RAS consists of a diffuse closed

network of excitatory and inhibitory interneurones lying along the rostrocaudal axis of the brain system. The excitatory interneurones of the RAS are believed to use glutamic acid as their neurotransmitter, and the inhibitory ones to use γ-aminobutyric acid (GABA). GABA is the principal inhibitory neurotransmitter in the central nervous system (62) and many hypnotic, sedative, anxiolytic, anti-epileptic, anti-spastic and anaesthetic drugs owe their activity to their effects on GABA-mediated neurotransmission (16).

Sleep is not a uniform process but consists of different phases, which are called sleep stages. Five are traditionally identified: I & II (light sleep), III & IV (deep sleep) and REM. During the night, several recurring sleep cycles occur, going from awake down through the first four sleep stages and back again. The deep stages III and IV, characterized by slow waves on the electroencephalogram (EEG), are considered to be the most restorative. The fifth sleep stage, REM sleep, is characterized by paradoxical EEG activity, vivid dreams, inhibited muscle tone, rapid eye movements, bursts of sympathetic activity and penile erections in males.

Although most people sleep for around seven hours each night, it is important to realize that some people function perfectly well on four hours sleep a night, whilst others require ten hours of sleep. This means that there is no normal or correct duration of sleep and thus that insomnia cannot be defined simply by a certain sleep duration. Instead, we can identify insomnia when an individual complains of not sleeping sufficiently long or well to function properly in the day.

Insomnia should be considered as a symptom of an underlying pathology, or of a change in life-style, rather than a disease in itself. Treatment should thus be directed primarily at resolving the underlying cause. Insomnia may be transient or chronic and may be characterized by difficulties in initiating or maintaining sleep. Impaired daytime functioning is the primary consequence of insomnia.

Different types of insomnia can be identified, dominated by difficulty in falling asleep, by early awakening or by multiple nocturnal awakenings.

The causes of insomnia are numerous and can be physical, such as pain or respiratory disease, psychological, such as stress or bereavement, psychiatric, such as depression or anxiety or pharmacological, such as alcoholism or benzodiazepine withdrawal (13, 24). Often, transient insomnia can be triggered by, for example, stress or illness, which then evolves into chronic insomnia, which persists even when the original trigger is removed.

Insomnia can be related to severe consequences including elevated mortality (31, 76), increased probability of having traffic accidents (1) and comorbility with psychiatric (20) and cardiovascular (22) disease. Several studies have demonstrated impaired quality of life in insomniacs (29) and there is generally a deterioration in social and professional relationships (26, 64, 11).

A major determinant of sleep quality is sleep hygiene (15). Poor sleep hygiene can trigger transient insomnia and favour the evolution of transient insomnia into chronic insomnia. The first-line treatment of insomnia should aim to improve sleep hygiene. This can be attempted by imposing regular bedtime and rising time, optimizing the sleeping environment and evening food intake, avoiding alcohol, caffeine and sugar also in the evening, as well as naps in the daytime and by taking physical exercise during the day.

3. Treatment of insomnia with hypnotics.

3.1 History

Hypnotic medication has been available since the introduction of chloral hydrate in the early nineteenth century. This was followed by the discovery and introduction of the barbiturates (1903), chlormethiazole (1958), the benzodiazepines (1961) and finally by zopiclone and zolpidem (1987/1988). All these drugs act by amplifying GABA-mediated neurotransmission in the brain.

The modern hypnotics in use today are the benzodiazepines such as (flunitrazepam, temazepam and triazolam) the cyclopyrolone zopiclone and the imidazopyridine zolpidem. These drugs are all extremely well tolerated compared to the previous generations of drugs, which had significant toxicity. In the vast majority of cases, they are the only hypnotic drugs that should be prescribed for the treatment of insomnia today. Benzodiazepines, zopiclone and zolpidem all interact with the same receptor in the brain, the α subunit of the GABA$_A$ receptor. In binding to this protein, they facilitate receptor activation by GABA (16).

3.2   The GABA$_A$ receptor: site of action of hypnotic drugs.

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the mammalian central nervous system (62). It inhibits neurons by interacting with an oligomeric protein in the cell membrane, the GABA$_A$ receptor. This protein is composed of five transmembrane peptide subunits arranged in a rosette. When the GABA$_A$ receptor is activateed by GABA, the peptide subunits move apart to form an ion-permeable pore across the membrane. This pore allows the passage of chloride ions across the membrane in response to the electrical gradient, which provides a short-circuit preventing the neuron from raisin an action potential (62). The GABA$_A$ reaptor is thought to be composed of two α subunits, two β subunits and one γ subunit (34). These differ in their amino acid composition and in their function. The β subunits are responsible for binding GABA, and thus initiating receptor activation (9). The α subunits bind benzodiazepines, zopiclone and zolpidem (34). Binding of hypnotic drugs to the α subunit increases the probability of channel opening in response

to GABA, and thus facilitates GABA-mediated inhibition (65).

There are several different isoforms of each of α, β and γ subunits whose presence in the receptor determines its pharmacological and biophysical properties (77). There are six different isoforms of the α subunit, α_1 to α_6. Receptors containing any of these isoforms recognize benzodiazepines and zopiclone, but only those containing α_1 have high affinity for zolpidem (49). GABA$_A$ receptors containing α_1 subunits have been referred to as BZ$_1$ or ω_1 subtypes, and those containing other α subunit isoforms BZ2 or ω2. The predominant form of native GABA$_A$ receptor in the mammalian brain has α subunit composition of α_1 β_2 γ_2 (40). The functional significance of GABA$_A$ receptor heterogenity and subtype colectivity remains unknown (17).

3.3 Absorption and elimination of hypnotic drugs.

The pharmacokinetic properties of hypnotic drugs are an extremely important determinant of therapeutic efficacy (23). A good hypnotic needs to be absorbed rapidly, to penetrate the brain and trigger sleep within thirty minutes of oral absorption of the drug. Plasma levels should remain sufficiently high to have pharmacological activity throughout the night and thus prevent nocturnal awakenings. Drug levels should have fallen below pharmacologically active levels when it is time to wake up, so that there are no residual sedative effects during the day. Drugs with very short half-life do not maintain their activity throughout the night (28), and may not prevent early awakenings. It has also been suggested (mainly from experience with triazolam) that such drugs may be more likely to produce dependence (28) and behavioral side effects (58, 42) during the day than longer-acting hypnotic drugs. Hypnotics with long half-life, on the other hand, will continue to be active the next day, producing sedation and impairment of cognitive performance (25). Difficulty waking up, and a muzzy feeling on waking (benzodiazepine hangover) may be experienced.

3.4 New generation hypnotic drugs:.

A. Zolpidem

Zolpidem is an hypnotic belonging to a new chemical class, the imidazopyridines, which are structurally unrelated to benzodiazepines. Zolpidem is a selective ligand for the central omega-1 receptor subtype with a high intrisic activity and a potent hypnotic effect. It has a low affinity for ω_1 (including α_2 or α_3 subunits) and no affinity for the peripheral BZD subtype. The ω_1 and ω_2 subtypes have specific central nervous system distribution; the ω_1 subtype being predominant in the cerebellum whilst both subtypes are present in the cerebral cortex and only the ω_2 subtype is present in the spinal cord. This specific affinity of zolpidem for the W1 subtype receptor results in marked hypnotic properties with only minor anxiolytic, myorelaxant and

anticonvulsant properties. Finally, zolpidem has a short elimination half life (2,5 hours) and no active metabolites, allowing a good hypnotic activity without residual effects in the morning (48).

Clinical material, involving both healthy volunteers and insomniac populations, has clearly demonstrated the hypnotic efficacy of zolpidem in daily doses ranging from 5mg to 20mg. Moreover, the sleep architecture generally remains unaffected at these dosages, apart from an enhancing effect upon slow-wave sleep (36, 41).

In two studies (69, 5) polysomnograpfic recordings showed that zolpidem and flunitrazepam (BZD) significantly shortened sleep onset latency. Zolpidem respected the overall sleep architecture, without disturbance of N-REM III and IV stages and REM sleep. Flunitrazepam significantly decreased REM sleep, slow wave sleep and increased stage II.

In a study with 1772 hospitalized insomniac patients, only 2,2% of them reported adverse events and less than 1% of them withdrew due to intolerance. 1,5% had their nightly dose reduced to 5mg/day due to adverse drug reactions. The most frequently reported were drowsiness, hangover, dizziness and nausea and nightmares and hallucinations (33). In healthy volunteers, zolpidem 10 or 20mg/day did not significantly alter respiratory parameters (35).

In a recent article (54) the author reviewed the literature to determine whether the behavioral pharmacologic profile of zolpidem also differs from that of benzodiazepines. The specific topics that are reviewed include abuse potential, tolerance producing effects and physiological dependence-producing effects. The most parsimonious conclusion is that despite its unique neuropharmacological profile, the behavioral effects of zolpidem are generally similar to those of benzodiazepines.

Another study (71) examined behavioral effects and development of physical dependence after once-daily increasing doses of zolpidem in three baboons. The conclusion was that zolpidem produced physical dependence and the severity of the withdrawal syndrome can be characterized as intermediate.

Other studies have shown that zolpidem, at a dose of 10mg, does not lead to dependence and that the side effects are rare and comparable to placebo (57, 74). It has also been shown that its pharmacokinetics are not altered by food, alcohol, caffeine and timing of administration (6).

Disturbances in psychomotor and cognitive functioning and memory have long been recognized to be associated with the use of hypnotic drugs, especially those that are eliminated slowly. Several classes of hypnotic drugs can affect next-day functioning and memory. Barbiturates, benzodiazepines and various over-the-counter drugs have all been shown to possess such properties, to varying degrees.

Next-day drowsiness or incoordination can be dangerous when performing tasks such as car driving or the operation of machinery and psychomotor impairment

may contribute to accidents. It is therefore important that hypnotic drugs should, as much as possible, be free from such undesirable "hangover" effects (69).

Morselli (43) reviewed double-blind studies involving observations made on the day after a single dose of 20mg zolpidem. Two studies included flunitrazepam as a positive control and two others triazolam. Despite using a higher dose than that currently recommended (10mg), measurements of saccadic eye movement peak velocity and repeated testing of daytime sleep latency showed that zolpidem did not affect alertness on the day after administration, although such an effect was clearly detected with the reference benzodiazepine. Next-day psychomotor function testing did not show any impairment of simple tasks. Creation time tests, digit symbol substitution tests etc.) after either zolpidem or triazolam, although a performance decrement was seen after flunitrazepam. In a more complex simulated driving test, zolpidem did not differ significantly from placebo, while triazolam measurably affected performance.

In another study (18) flunitrazepam significantly impaired attention and memory compared with zolpidem and placebo, while zolpidem did not differ from placebo the day after administration.

The more recent studies (14, 68) also reach the conclusion that, at the clinically recommended dose (10mg), zolpidem treatment appears to give rise to no, or minimal next-day effects on psychomotor and cognitive functions.

Many studies showed that zolpidem is capable of impairing both memory and psychomotor functions near the time of peak plasma concentration. These effects, behavioral and subject-rated, are similar to those of benzodiazepine hypnotics and zopiclone (55, 2).

Another study (75) concluded that there was no significant interaction between zolpidem and alcohol, which did not potentiate the performance-impairing effects of zolpidem in the time of peak plasma concentration.

The literature on this is, however, inadequate, and further research is needed to determine whether consumption of alcohol is safe in combination with 3rd generation hypnotics.

The sedative effects of 10mg of zolpidem are not antagonized be 150-300mg of caffeine in pharmacodynamic or pharmacokinetic terms (37).

Another study (72) showed that flumazenil (1,0mg) a benzodiazepine receptor antagonist, can reverse memory impairment caused by agonists of the benzodiazepine receptor, like triazolam and zolpidem.

B. Zopiclone

Zopiclone is an hypnotic with a short half-life (5 hours) which was demonstrated efficacy in sleep quality as accessed by questionnaires (46).
A number of comparative studies with benzodiazepine hypnotics, including flunitrazepam, flurazepam, nitrazepam, triazolam and temazepam, in insomniac patients have not identified significant differences in

perceived sleep quality between zopiclone and the benzodiazepines (44, 70). In EEG studies, deferences between zopiclone and certain benzodiazepine hypnotics have been observed. The most important of these is that zopiclone does not appear to decrease the time spent in slow-wave sleep and in REM sleep (44, 70). In some (but by no means all) of these studies, zopiclone actually increases the time spent in these sleep phases.

Morning-after effects of zopiclone are mild compared to most BZD hypnotics (70). Subjective assessment of alertness the next morning in insomniacs generally has shown zopiclone (7,5mg) to be superior to nitrazepam (5 or 10mg), flurazepam (30mg) and flunitrazepam (1 or 2mg). Impairment of psychomotor performance after zopiclone, however, has been demonstrated objectively in some, but not all, studies in healthy volunteers (32, 7).

In a comparative study (45) with zopiclone, flunitrazepam and nitrazepam, all three drugs induced some impairment of memory, but effects were more pronounced with the two benzodiazepines and especially flunitrazepam.

The adverse events seen with zopiclone are bitter taste, dry mouth, drowsiness, dizziness, tiredness, lack of coordination, depression and headache.

We conclude that zolpidem, because of its very short half-life, has better results in measures of next-day psychomotor performance and memory than zopiclone. A drawback of the short half-life is that the hypnotic effect may wane during the night, leading to a deterioration of sleep quality towards the end of the night. A similar phenomenon has been reported for short-acting benzodiazepine hypnotics (28). In contrast, zopiclone provide significantly fewer spontaneous awakenings (52).

Caffeine moderately antagonizes the effects of triazolam and zopiclone on the psychomotor performance of healthy subjects (45). But zopiclone counteracted the effects of caffeine more easily than caffeine counteracted the decremental effects of zopiclone.

In another study (30) the authors studied the co-administration of alcohol with zopiclone and triazolam (BZD). Alcohol enhanced and prolonged the effects of both hypnotics without modifying their plasma concentrations. Drug-alcohol interactions were mainly additive though more obvious with TRZ. The hypnotics were free from residual psychomotor and cognitive effects at 8h even after the co-administration of alcohol.

In another study (4) the authors interpreted their findings as suggesting that the users of anxiolytic benzodiazepines and zopiclone were at increased risk of road-traffic accidents.

Finally there is a report (3) of physical dependence on zopiclone in individuals with depended personalities.

In this table we can see the main properties of hypnotic drugs :

	ZOLPIDEM	ZOPICLONE	BENZODIAZEPINES half life Short (TRIAZ)	Long (FLU)
1.Efficacity to induce sleep	+	+	+	+
2.Sleep quqlity	+	+	+	+
3.Anxiolytic Myorelaxant Anticonvulsant	-	+	++	++
4.Elimination longlife	2,5 h	5 h	1 -4 h	20 h
5.Adverse events	+	++	+++	+++
6.Spontaneous awakenings	+	-	+	-
7.Residual effects in the morning	-	+	-	++
8.Disturbances of sleep architecture	-	+/-	++	++
9.Next day pshychomotor performance	++	+	+	-
10.Caffeins antagonizes	-	+	++	++
11.Alcohol interaction	+/-	+	++	++
12.Dependence Tolerance effects Abuse potential	+	+	+++	++

C. Antihistamines and antidepressants.

The antihistamines do not increase total sleep time, but offer a shorter sleep latency period. Side effects of residual daytime sedation are well documented. The antidepressants have a long half-life and residual daytime effects.

D. Melatonin.

Several studies suggest that melatonin may produce behavioral sedation or facilitate objectively measured sleep, others have found no appreciable effect. There are theoretical reasons to be concerned about its use: melatonin is vasoconstrictive and has unwanted disruptive effects on reproductive endocrine function.

3.5 Hypnotic drug use in military operations.

A French study (60) examined the action of 10mg of zolpidem and 1mg of flumitrazepam compared to placebo in 12 pilots and 12 ground personnel. The subjects underwent psychomotor testing in a flight simulator and spectroscopic EEG analysis.

Sleep quality was similar after administration of zolpidem and flumitrazepam. The ground personnel who received benzodiazepines showed difficulty in walking, somnolence and lack of energy compared to those receiving zolpidem or placebo. On the contrary, no differences were found, either in self-assessments or in psychomotor testing, in pilots. This can be explained by the fact that pilots are highly motivated and therefore able to overcome certain potentially adverse factors.

The EEG analysis showed no effect of zolpidem, while those receiving benzodiazepines had a greater prevalence of slow waves, reduction of the a rhythm, and development of fast rhythms.

Other studies (66) have shown that zopiclone, zolpidem and temazepam do not influence athletic performance. A U.S. army Aeromedical Research Laboratory study (8) compared the effects of zolpidem-induced prophylactic naps and forced rest periods in prolonged work schedules. The conclusion was that zolpidem-induced naps were more effective because the subjects obtained more sleep after zolpidem administration. Post-nap grogginess persisted for about 2 hours after either the zolpidem or placebo nap, a fact which, despite the overall benefits from prophylactic naps, could compromise performance under operational conditions if insufficient time for awakening was planned.

Another study (50) concluded that zolpidem is a hypnotic which appears to cause less global impairment than benzodiazepine during peak effect, and is free of persistent performance decrement or hangover effect.

A study of the influence of daytime administration of zolpidem and triazolam on performance showed that there is no advantage of zolpidem over triazolam (63) in performance-impairing effects.

Finally, it was shown that zolpidem improved sleep quality at high altitute (4.000 meters) without affecting respiration (5).

CONCLUSIONS

It is evident from the above that 3rd generation hypnotics (zolpidem and zopiclone) do have some advantages over the older benzodiazepines, primarily because they do not significantly influence higher cognitive functions the day after the administration. Specifically, zolpidem is free of any such influence 6 hours after administration, while the same may be true of zopiclone a few hours later due to its longer half-life.

These new hypnotics also facilitate the easy achievement of good quality sleep, as they do not disrupt its architecture and allow both deep stages III and IV sleep, which is necessary for adequate rest, and REM sleep, which is necessary for dreaming, a process fundamental for the psychological well being.

The side effects are very few but the possibilities of some form of dependence and of synergistic effect with alcohol have not been adequately studied yet. We do not have many studies concerning these issues but the few which exist, give encouraging results.

Most studies, about the use of drugs in military operations, are performed in simulated conditions, which do not fully reproduce the stress of an actual operation (the presence of enemy, loss of companions, unfamiliar and/or hostile environment). Moreover, they do not take into account the pilot's psychological profile and any human weaknesses. Despite the progress of psychopharmacology, chemically induced sleep cannot match the quality of normal sleep and a pilot who needs a drug to get an adequate rest may induce the psychological perception of a dependent person.

Observations from military Air Forces have shown that pilots may occasionally try to confront their stress with alcohol. What could then be the effect of co-administration of a drug and how can the complete absence of a synergistic effect be guarantied? Could the flight surgeon be seen as co-responsible of an accident? Another possibility is that the pilot may, depending on the time and composition of the last meal be at risk of relative hypoglycemia or he may not be at the peak of his health during the operation. What would be the effect of drug administration then?

Also, there should be an urgent operational need, when the drug is near its peak concentration, when the pilot will clearly be unsuitable.

Frequent nocturnal operations disrupt circadian rhythms. In order to deal with this an adequate number of pilots must be required to allow sufficient time for rest and to alternate participation in operations.

Finally, let us not forget that a real combat situation brings to the surface all the aspects of somebody's personality. We are not dealing with a car engine, which regularly needs lubrication for optimum functionality, but with human beings that (may) have ethical dilemmas regarding their mission. Consciences are not determined by propaganda and may revolt particularly when risks of civilian casualties are high. Let us not forget that one of the three Enola-Gay pilots became insane after the bombing of Hiroshima.

REFERENCES

1) *Aldrich MS.*
Automobile accidents in patients with sleep disorders. Sleep 12: 487-494, 1969.

2) *Allain et al.*
Comparative study of the effects of zopiclone (7,5mg), zolpidem, flunitrazepam and a placebo on noctural cognitive performance in healthy subjects, in relation to pharmacokinetics. Eur.Psychiatry 10(suppl.3): 129s-135s, 1995.

3) *Ayorinde O, Sampson E.*
Psysical dependence on zopiclone. Risk of dependence may be greater in those with dependent personalities. BMJ 11: 317(7151): 146, Jul. 1998.

4) *Barbone F et al.*
Association of road-traffic accidents with benzodiazepine use. Lancet 24: 352 (9137): 1331-6, Oct. 1998.

5) *Beaunont M et al.*
Effect of zolpidem on sleep and ventilatory patterns at simulated altitude of 4.000 meters. Am.J.Respir.Crit.Care Med. 153(6Pt 1): 1864-9, Jun. 1996.

6) *Bianchetti G et al.*
Clinical pharmacokinetics of zolpidem in various physiological and pathological conditions. Sauvanet JP., Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders.New York, Raven Press, 155-163, 1988.

7) *Broadhusrt A, Cushnaghan RC.*
Residual effects of zopiclone (Imovane). Sleep 1987; 10 (suppl.1): 48-53.

8) *Cadwell JA et al.*
Comparison of the effects of zoplidem-induced prophylactic naps to placebo naps and forced rest periods in prolonged work schedules. Sleep 21(1): 79-90, 1998.

9) *Casalotti SO, et al.*
Separate subunits for agonists and benzodiazepine binding in the γ-aminobutyric acid a receptor oligomer. J Biol Chem 261: 15013-15016, 1986.

10) *Chidester Tr.*
Trends and individual differences in response to short – haul flight operations. Aviat. Space Environ.Med. 61: 132-138, 1990.

11) *Chilcot L.A., Shapiro CM.*
The socioeconomic impact of insomnia. An overview. Pharmacoeconomics 10(suppl.1): 1-14, 1996.

12) *Clausen O.P., et al.*
Circadian rhythms in mouse epidermal basal cell proliferation, variations in comportment size, flux and phase duration. Cell Tissue Kinet.12: 319-337, 1979.

13) *Coleman R., et al.*
Sleep-Wake disorders based on a polysomnographic diagnosis: a national cooperative study. JAMA 247: 997-1003, 1982.

14) *Declerck AC, Bisserbe JC.*
Short-term safety profile of zolpidem: objective measures of cognitive effects.Eur.Psychiatry 12 (suppl.1): 15s-20s, 1997.

15) *Dement W.C., Mitler MM.*
It's time to the importance of sleep disorders. JAMA 269: 1548-1549, 1993.

16) *Doble A., Martin IL.*
The GABA$_A$ benzodiazepine receptor as a target for psychoactive drugs. Springer Verlog, Heidelberg; 1996.

17) *Doble A., Martin IL.*
Multiple benzodiazepine receptors: no reason for anxiety. Trend Pharmacol Sci 13: 76-81, 1992.

18) *Dujardin et al.*
Comparison of the effects of zolpidem and flunitrazepam on sleep structrure and daytime cognitive functions. A study of untreated insomniacs. Pharmacopsychiatry 31 (1): 14-18, Jan 1998.

19) *Dujardin K., et al.*
Sleep, brain activation and cognition. Phyxiol. Behav. 47: 1271-1278, 1990.

20) *Ford DE., Kamerow D.B.*
Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 262: 1479-1484, 1989.

21) *Fossen A., et al.*
Effects of hypnotics on memory. Pharmacology 27 (suppl.2): 116-126, 1983.

22) **Gislason T-, Almaqvist M.**
Somatic diseases and sleep complaints. An epidomeiological study of 3201 Swedish men. Acta Med Scand 221: 475-481, 1987.

23) **Greenblatt DJ et al.**
Neurochemical and pharmacokinetic correlates of the clinical action of benzodiazepine hypnotic drugs. Am.J.Med. 88: 18s-24s, 1980.

24) **Hauri P.J., Esther M.S.**
Insomnia Mayo Clin.Proc. 65: 69-882, 1990.

25) **Hindmarch I.**
Effects of hypnotic and sleep. Inducing drugs on objective assessments of human psychomotor performance and subjective appraisals of sleep and early morning behaviour. Br.J.Clin.Pharmacol. 8: 43s-46s, 1979.

26) **Johnson L.C., Spinweher C.L.**
Good and poor sleepers differ in navy performance. Mil.Med. 148: 727-731, 1983.

27) **Jouvet M.**
Neurophysiology of the stages of sleep. Physiol. Rev. 47: 17-117, 1967.

28) **Kales A., Soldatos Cr. et al.**
Early morning insomnia with rapidly eliminated benzodiazepines. Science 220:95-97, 1983.

29) **Kelly F., et al.**
Quality of life and insomnia. Results of the validation studies for a specifically designed questionnaire. JAMA SCA 9 (suppl) : 21-36, 1993.

30) **Kiutunen T et al.**
Actions and interactions of hypnotics on human performance: single dose of zopiclone, triazolam and alcohol. Int.Clin.Psychopharmacol. 5 (Suppl. 2): 115-130, Apr. 1990.

31) **Kripke D.F., et al.**
Short and long sleep and sleeping pills. Is increased mortality associated?
Arch.Gen.Psychiatry 36: 103-116, 1979.

32) **Lader M., Denney SC.**
A double-blind study to establish the residual effects of zopiclone on performance in healthy volunteers. Pharmacology 27 (suppl.2) : 98-108, 1983.

33) **Licciardello L., Licini P.**
Safety and efficacy of zolpidem therapy in sleep disorders: a multicenter trial in hospitalized patients. Card.Ther.Res. Clin.Exp. 52: 652-8, 1992.

34) **Macdonald RL, Olsen RW.**
GABA$_A$ receptor channels. Annu Rev. Neurosci 17: 569-602, 1994.

35) **Maillard D., et al.**
Effects of zolpidem versus diazepam and placebo on breathing control parameters in healthy human subjects and heavy snorers. Int.J.Clin. Pharm. Res. 12: 27-35, 1992.

36) **Maarek, et al.**
The safety and efficacy of zolpidem in insomniac patients: a long term open study in general practice. J.Int. Med.Res. 20: 162-170, 1992.

37) **Mattila MJ et al.**
Zolpidem 10mg given at daytime is not antiagonized by 300mg caffeine in man. Eur.J.Clin.Pharmacol. S4(5): 421-5, jul 1998.

38) **Maquet P.**
Positron emission tomography studies of sleep and sleep disorders. J.Neurol. 244 (suppl 1), S 23 –S 28, 1997.

39) **McCauley SF.**
Aircrew fatigue counter-measures in AGARD, Progress in Millitary Airlift GP,11 1-11.6, dec 1990.

40) **Mc Kernan RM, Whiting PJ.**
Which GABAA –receptor, subtypes really occur in the brain? Trends Neurosci 19: 139-143, 1996.

41) **Monti J.**
Effects of zolpidem on sleep in insomniac patients. Eur. J Clin. Pharmacol.36: 461-466, 1989.

42) **Morgan K., Oswald I.**
Anxiety caused by a short half-life hypnotic BMJ 284: 942, 1982

43) **Morselli PL, et al.**
Daytime residual effects of zolpidem: a review of available data. In Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders. New York: Raven Press, 339-349, 1988.

44) **Musch B, Maillard F.**
Zopiclone, the third generation hypnotic: a clinical overview. Intl.Clin.Psychopharmacol. 5 (suppl 2): 147-158, 1990.

45) **Nattila ME et al.**
Caffeine moderately antagonizes the effects of triazolam and zopiclone on the psychomotor performance of healthy subjects. Pharamacol.-Toxicol. 70(4) : 286-9, Apr. 1992.

46) **Nair NPV et al.**
A dose-range finding study of zopiclone in insomniac patients. Intl.Clin.Psychopharmacol. 5 (suppl.2): 1-10, 1990.

47) **Nicholson A.N.**
Long range air capability and the south Atlantic compaign. Aviat.Space Environ. Med. 55: 269-270, 1984.

48) **Priest RG.**
Efficacy of zolpidem in insomnia. Eur.Psychiatry 1995.

49) **Pritchett DB et al.**
Type I and Type II GABA$_A$-benzodiazepine receptors produced in trandfected cells. Science 245: 1389-1392, 1989.

50) **Ramsey CS et al.**
Zolpidem as a fatigue countermeasure. Aviat.-Space-Environ.Med. 68(10): 926-31, oct. 1997.

51) **Reeve DR.**
A study of mitotic activity and the diurnal variation of the epithelial cells in wounded rectal mucous membrane. J.Anat. 119: 333-345, 1979.

52) **Rettig HC et al.**
Effects of hypnotics on sleep and psychomotor performance. A double-blind randomised study of

lormetazepam, midazolam and zopiclone. Anaesthesia 45(12): 1079-82, Dec 1990.

53) Roscol AH.
Pilot arousal during the approach and landing. Aviat. Med. Quaterly 1: 31-36, 1987.

54) Rush CR.
Behavioral pharmacology of zolpidem relative to benzodiazepines: a review. Pharmacol. Biochem. Behav. 61: (3) : 253-269, Nov. 1998.

55) Rush CR, Griffiths RR.
Zolpidem, triazolam and temazepam: behavioural and subject – raked effects in normal volunteers. J.Clin. Psychopharmacolo. 16(2): 146-157, 1996.

56) Salin – Pascual RJ et al.
Long-term study of the sleep of insomnia. Patients with state misperception and other insomnia patients. Am J. Psychiatry 149: 904-908, 1992.

57) Sauvanet J.P. et al.
Open long term trials with zolpidem in insomnia. Sauvanet J.P., Langer SZ, Morselli PL., eds. Imidazopyridines in sleep disorders. New York Raven Press, 339-349, 1988.

58) Scharf MB et al.
Comparative amnestic effects of benzodiazepine hypnotic agents. J.Clin. Psychiat. 49: 134-137, 1988.

59) Senechal P.K.
Flight surgeon support of combat operations at RAF Upper Heylord. Aviat-Space Environ. Mcd. 59: 776-777, 1980.

60) Sicard B.et al.
Evaluation des effects du zolpidem sur la vigilance et les capacités psychomotrices du personnel au sol et des pilotes. Med Aéronautique i spaciale. Tone XXXIII No 131: 169-174, 1994.

61) Simmons D. et al.
Biorhythmic profiles in the rat skeleton. Metab. Bone Relat. Res. 2: 49-64, 1979.

62) Sivilotti L., Nistri A.
GABA receptor mechanisms in the central nervous system.Prog. Neurobiol. 36: 35-92, 1990.

63) Steriade M.
Arrousal: revisiting the reticular activating system. Science 272: 225-226, 1996.

64) Stoller M.K.
Economic effects of insomnia. Clin.Ther. 16: 873-897, 1994.

65) Study R.E., Barker JL.
Cellular mechanisms of benzodiazepine action. JAMA 247: 2147-2151, 1982.

66) Tafti M et al.
Effects of zopiclone on subjective evaluation of sleep and daytime alertness and on psychomotor and physical performarce tests in athletes. Prog.Neuropsychopharmacol. Biol. Psych. 16(1): 55-63, Jan 1992.

67) Takahashi Y., et al.
Growth hormone secretion during sleep. J.Clin Invest 47: 2079-2090, 1968.

68) Unden M., Roth Schechter B.

Next day effects after nighttime treatment with zolpidem: a review. Eur.Psychiatry 11(suppl.1): 21s-30s, 1996.

69) Vermeeren A., O' Hanlon J.F.
Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. Acta Therapeutica 21: 47-64, 1995.

70) Wadworth AN, Mc Tavish D.
Zopiclone: a review of its pharmacological properties and therapeutic efficacy as on hypnotic. Drugs. Aging 3: 441-459, 1993.

71) Weerts E.M. et al.
Zolpidem physical dependance assessed across increasing doses under a once-daily dosing regimen in baboons. J.Pharmacol.Exp. Ther. 285(1): 41-53, 1998.

72) Wesesten NJ et al.
Reversal of triazolam,-and zolpidem–induced memory impairement by flumazenil. Psychopharmacology-Berl 121 (2): 242-9, 1995.

73) Wesesten et al.
Effects of daytime administration of zolpidem and triazolam on performance.Aviat. Space Environ. Mcd. 67(2): 115-20, Feb. 1996.

74) Wheatley D.
Zolpidem and placebo: a study in general practice in patients suffering from insomnia. Sauvanet JP., Langer JZ, Morselli PL. eds. Imidazopyridines in sleep disorders. New York, Raven Press, 305-316, 1988.

75) Wilkinson CJ.
The acute effects of zolpidem adiministered alone and with alcohol, on cognitive and psychomotor function. J.Clin.Psychiatry 56(7): 309-318, jul 1995.

76) Wingard D.L., Berkman L.F.
Mortality risk associated with sleeping patterns among adults. Sleep 12: 487-494, 1969.

77) Wisden W., Seeburg PH.
GABA$_A$ receptor channels: from subunits to functional entities. Cur.Opin.Neyrobiol. 2: 263-269, 1998.